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(57) Abstract

Calcium antagonists and compounds which lower intraocular pressure are combined in ophthalmic compositions to treat glaucoma. The calcium antagonists prevent or reduce the loss of visual field, while the intraocular pressure-lowering compounds maintain the intraocular pressure at normal levels.

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TOPICAL OPHTHALMIC COMPOSITIONS COMPRISING A COMBINATION OF CALCIUM ANTAGONISTS WITH KNOWN ANTIGLAUCOMA AGENTS

Background of the Invention

The present invention relates generally to the field of ophthalmology. In particular, the invention relates to the treatment of glaucoma using a combination of a compound which lowers intraocular pressure (IOP) and a calcium channel antagonist to prevent or reduce the loss of visual field.

Although the underlying causes of glaucoma are not understood at this time, glaucoma is characterized by damage to the optic nerve, accompanied by a decrease in the normal visual field. One early warning sign of possible glaucomatous visual field loss is elevated IOP. In fact, glaucoma has historically been treated by medically and/or surgically lowering elevated IOP. However, elevated IOP does not always result in the occurrence of visual field loss; moreover, visual field loss may occur at levels of IOP which are considered within the normal range. Thus, factors other than IOP play a role in determining the occurrence of visual field loss. Microcirculatory disturbances which restrict nutritive blood flow to the choroid, retina and optic nerve fibers are undoubtedly also involved.

Summary of the Invention

The present invention provides compositions useful in the treatment of glaucoma and ocular hypertension. The compositions contain a combination of at least one calcium channel antagonist and at least one compound which lowers IOP. The combination is effective in reducing or preventing visual field loss, as well as reducing IOP to normal levels. Further, the reduction of IOP provides both the patient and the physician with an easy means of tracking a patient's progress.

In an alternate embodiment of the compositions of the present invention, the above combination may further include an anionic mucomimetic polymer, a gelling polysaccharide, a finely divided drug carrier substrate (defined below), or a combination of these components. These additional components provide compositions which are comfortable and have sustained release.

Detailed Description of the Invention

To remain healthy and function normally, the retina and the optic nerve fibers (neurons) must receive a proper supply of nutrients and oxygen and must have their metabolic waste products and carbon dioxide removed. This is accomplished by the microcirculation of these tissues. As used herein, the term "microcirculation" refers to the blood flow through the nutritive blood vessels, across whose walls nutrients, gases and waste products move. Blood flow to the eye depends upon the perfusion pressure (the systemic blood pressure minus the IOP). Blood pressure is partially determined by the caliber of the blood vessel lumen, which is due to the degree of contraction of the vascular smooth muscle (the vascular tone). A reduction of the caliber of the vessel lumen causes a decrease in the blood flow, related to the vessel's cross-sectional diameter. Ischemic vasoconstriction (ischemia) is a condition wherein the oxygen supply to a tissue is severely decreased as a result of marked decrease in blood flow. Prolonged ischemia can result in the necrosis, or death, of tissue. In the case of neuronal tissue such as the optic nerve, a state of dysfunction may precede the death of the neurons. If ischemia is involved in the death of optic nerve fibers which occurs with glaucoma, then its prevention could protect the neurons from death and loss of function.

Vasoconstrictive substances cause a decrease in vessel diameter, while vasodilative substances cause the opposite effect. Among the known vasoconstrictors in the body are the following: angiotensin II, norepinephrine, serotonin, vasopressin and endothelin. The local constriction of blood vessels

supplying the retina and optic nerve can result in decreased blood flow to the tissues and marked vasoconstriction induced by vasoconstrictive substances can result in ischemia.

Calcium plays a key role in the regulation of intracellular processes. Calcium ion exists in extracellular and intracellular fluids and is found in bound and free forms. Calcium regulates the actin-myosin-ATP interaction which is involved in vascular smooth muscle contraction. Calcium antagonists are known to inhibit potential-operated and receptor channels, thereby preventing the movement of extracellular calcium into the cell and vascular smooth muscle contraction. Some calcium antagonists have been shown to inhibit myogenic activity in vascular smooth muscle. Calcium antagonists can prevent ischemic vasoconstriction by decreasing calcium flux into the sarcoplasmic reticulum of vascular smooth muscle cells. Therefore, calcium antagonists can be beneficial to treat ischemia of the retina and optic nerve tissues that may be present in glaucoma patients.

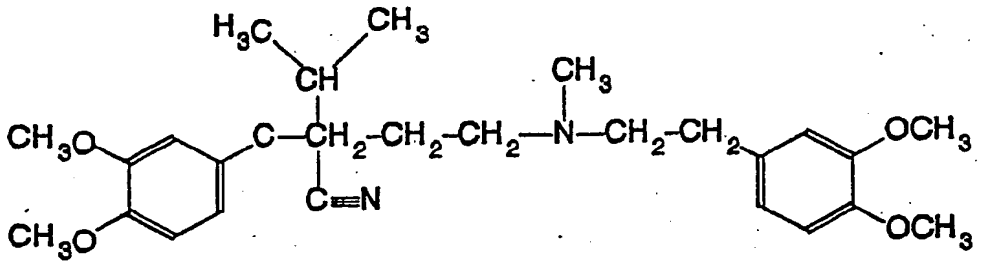
Furthermore, aside from its involvement in ischemic vasoconstriction, calcium plays a more direct role in the death of cells and tissues. During ischemia, calcium is translocated from the extra- to the intra-cellular fluid which may result in the sequestration of calcium by mitochondria. Furthermore, glutamate-gated calcium channels and voltage-regulated calcium channels can open during activation by glutamate or depolarization of retinal ganglion cells, respectively, which can result in a dramatic rise of calcium in the cell cytosol. Calcium overload of retinal ganglion cells can result in cell death and neuronal degeneration. In ischemia, calcium antagonists can protect mitochondria against calcium overload and preserve mitochondrial ultrastructure and function. The excitatory amino acid, glutamate, has been implicated in neurotoxicity, and causes depolarization of retinal ganglion cells; however, this is not sufficient to cause neurotoxicity. Neuronal cell death following glutamate-induced injury has been observed in the presence of calcium ion in the bathing medium. Thus, the prevention of calcium flux into neuronal and retinal cells may directly offer protection against damaging result of ischemia.

Calcium antagonists are compounds which modulate the channels that conduct calcium between the outside and the inside of cells. Their major action is to modulate the entry of calcium into the cell. As calcium is involved in the process of vascular contraction, calcium antagonists can interfere with this process and modulate contraction. By decreasing the degree of vascular contraction, calcium antagonists bring about vasodilation, i.e., an increase in the caliber of the blood vessel lumen. Also, to the extent that calcium influx is deleterious to the cell, calcium antagonists can ameliorate this situation and preserve the cell against death. In ischemia, calcium antagonists can protect mitochondria against calcium overload and preserve mitochondrial ultrastructure and function. Therefore, calcium antagonists can have a double benefit to tissues experiencing vasoconstrictive ischemia. First, they can cause vasodilation to increase blood flow and counter the ischemic conditions; second, they can protect the cell from the deleterious effects of calcium overload which occurs under the ischemic condition. Since lowering IOP also favors an increase in ocular blood flow, the combination of a calcium antagonist and an IOP-lowering compound will have a broader protective action than either one alone.

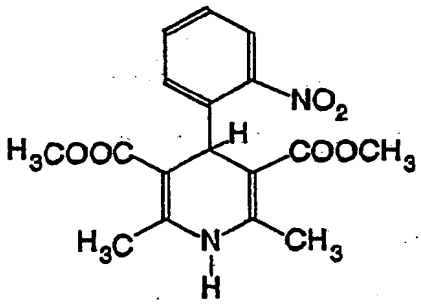
The calcium antagonists which are useful in the present invention include all presently known calcium antagonists, especially those which show a selectivity towards neuronal and/or retinal vascular calcium channels. In particular, it is better if the calcium antagonist does not significantly lower the systemic blood pressure while exerting its blockade of calcium channels in optic nerve tissue, as that would reduce the ocular perfusion pressure and tend to reduce ocular blood flow. Further, those calcium antagonists which have a myocardial depressant action would be less preferred due to their potential for causing a side effect on the heart.

Such calcium antagonists can be typically divided into three chemical classes: 1,4-dihydropyridines, such as nifedipine, nisoldipine, nimodipine, nicardipine, nitrendipine and niludipine; arylalkylamines, such as verapamil, prenylamine, fenidiline, bepridil, falipamil, tiapamil, gallopamil, and bencyclane; and benzothiazepines, such as diltiazem, cinnarizine, flunarizine and lidoflazine.

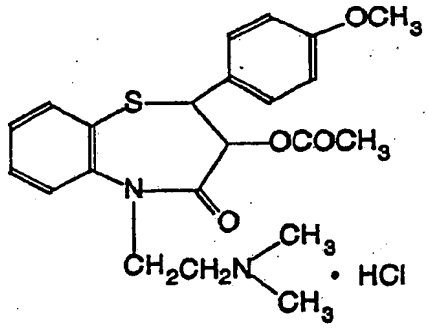
Representative calcium antagonists for each of the three chemical classes are shown below in Structures (I) through (III).



(I) VERAPAMIL



(II) NIFEDIPINE



(III)DILTIAZEM

The preferred calcium antagonists are the enantiomeric and racemic forms (where applicable) of: AE 0047, AHR 5360C, AHR 12234C, AHR 16303B, AHR 16462B, AJ 2615, AJ 3941, AQ-AH-208-Cl, AR 12-456, alismol, amlodipine, anipamil, B 844-39, Bay-e-6927, Bay-k-9320, barnidipine, BBR 2160, belfosdil, benidipine, bepridil, bisaramil, BMY 20014, BMY 20064, BN 50149, BN 50175, BN 50394, BRL 3287A, buflomedil, butoprozine, caroverine, CD 349, CERM 11956, CGP 22442, CGP 26797, CGP 28392, CGP 28727, CGP 32413, CGS 19755, CI 951, cinnarizine, CNS 2103, COR 28-22, COR-2707C, COR 3752C, cronidipine, CRE 202, CRE 204, CRE 1005, CS 905, CV 159, D 2603, dagapamil, darodipine,

desmethylverapamil, DHM9, DHP 218, diclofurime, diltiazem, diperdipine, diproteverine, dopropidil, dotarizine, EG 1088, elgodipine, emopamil, F-0401, fantofarone, FCE 24265, fedopamil, felodipine, feniline, flordipine, flunarizine, fostidil, FPL 62129, FR 46171, FRC 8411, FRG 8653, furaldipine, gallopamil, GOE 5057, GOE 5584-A, GOE 93007, GYKI 46544, HA 1004, HA 1077 (cerebroarterial selective), HE-3-0346, HOE-166, Hoe 263, HP 406, israldipine, KB 2796, KP 873, KT 362 (inhibs intracellular Ca), KW-3049 (benidipine), KW 3049-vasculoselective, lacidipine, LAS 30356, LAS 30398, LAS 30538, LAS-Z077, LCB 2514, lidoflazine, LU 49938, manidipine, MCI 176, McN 5691, McN 6186, MCN 6497, MD 260792, MDL 143, MDL 12330A, MDL 16582A, MDL 72567, mepami, mepirodipine, mesudipine, minodipine, mioflazine, MJ 14712, MPC 1304, MPC 2101, N 20776, naltiazem, NB 818, NC 1100, NCO 700, NH 2250, NH 2716, NKY 722, NP 252, NZ 105, nicardipine, nictiazem, nifedipine, nigludipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, OPC 13340, oxodipine, P 0285, palonidipine, P 1268, PD 122860, pelanserin, perhexiline, PF 244, pirprofurol, pimozide, PN 200-110, prenylamine, R 71811, Rec 15/2288, Rec-15/2375, RGH 2970, riodipine, Ro 18-3981, Ro 40-5967, ronipamil, RS 93007, RU 43945, RWJ 22726, RWJ 26899, RWJ 26902, ryanodine, S 312-d, S12968, S11568, S 830327, SA 2572, SA 2995, SA 3212, sagandipine, SC 30552, selodipine, semotiadil, SIM 6080, SKF 96365, SM 6586, somidipine, SL 85.1016, SQ 31486, SQ 31765, SQ 31727, SQ 32321, SQ 32324, SQ 33351, SQ 33537, SR 33805, SUN 5647, SUN 6087, TA 3090 (clentiazem), taludipine, tiapamil, TN 871, TR 2957, trapidil, UK 51656, UK 52831, UK 55444, verapamil, vinigrol, vintoperol, W 787, WAS 4206, WK 269, WY 27569, WY 44644, WY 44705, WY 46622, WY 47324, Y 19638, Y 208835, Y 22516, YC 114, YM 15430-1, YM 16151-4, YS 035, and YS 161, as well as their pharmaceutically acceptable salts. Most preferred are: bluflomedil, diltiazem, emopamil, felodipine, flunarizine, israldipine, lidoflazine, mioflazine, nimodipine, nifedipine, R-56865 and R-58735.

The IOP-lowering compounds useful in the present invention include all presently known IOP-lowering compounds, including miotics (e.g., pilocarpine,

carbachol and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine, dipivalylepinephrine and para-amino clonidine); beta-blockers (e.g., betaxolol, levobunolol and timolol); and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide). The preferred IOP-lowering compounds are: timolol, betaxolol, levobunolol, carteolol, pilocarpine, carbachol, MK 927, MK 507, AL04414, ALO4623, ALO4862, epinephrine, dipivalyl epinephrine, α-methyl dipivalylepinephrine, apraclonidine, clonidine.

In general, an amount of a calcium antagonist between about 0.0001 and about 10.0 percent by weight (wt%) and an amount of an IOP-lowering compound between about 0.00001 and about 10.0 wt%. It is preferred that an amount of a calcium antagonist between about 0.001 and about 5.0 wt% is used and it is especially preferred to use an amount between about 0.01 and about 2.5 wt%. An amount of an IOP-lowering compound between about 0.001 and about 5.0 wt% is preferred and an amount between about 0.01 and about 2.5 wt% is especially preferred. The ratio by weight of calcium antagonist to IOP-lowering compound is generally between about 100:1 to about 1:100, preferably between about 10:1 to about 1:10.

The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Patent No. 4,911,920 issued 27 March 1990, and in EP 507 224 A1 (published 7 October 1992). The entire contents of that patent and patent application are incorporated herein by reference.

The high molecular weight, anionic mucomimetic polymers useful in the present invention have a molecular weight between about 50,000 and 6 million daltons. The polymers are characterized as having carboxylic acid functional groups and preferably contain between 2 and 7 carbon atoms per functional group. The gels which form during preparation of the ophthalmic polymer dispersion have

a viscosity between about 1,000 to about 300,000 centipoise (cps). Suitable polymers are carboxy vinyl polymers, preferably those called Carbomers, e.g., Carbopol® (B.F. Goodrich Co., Cleveland, Ohio). Specifically preferred are Carbopol® 934 and 940. Such polymers will typically be employed in an amount between about 0.05 and about 8.0 wt%, depending on the desired viscosity of the composition. Pourable liquid compositions generally comprise an amount of the polymer between about 0.05 and about 2.0 wt%.

As used herein, the term "finely-divided drug carrier substrate" (or "DCS") means finely-divided solids, colloidal particles, or soluble polymers and/or polyelectrolytes which are capable of selective adsorption or binding with drug molecules. Examples of DCS include, but are not limited to: finely divided silica, such as fumed silica, silicates and bentonites; ion exchange resins, which can be anionic, cationic or non-ionic in nature; and soluble polymers, such as, alginic acid, pectin, soluble carrageenans, Carbopol®, and polystyrene sulfonic acid. In general, the DCS component is used at a level in the range of about 0.05 to about 10.0 wt%. For particulate DCS, the average particle size diameter ranges from 1 to 20 microns. The amount of DCS and its characteristics (e.g., amount of cross-linking, particle size) may be varied in order to produce the desired time-release profile for the chosen drug.

Preferred DCS are the ion exchange resins. Some resins which are used in chromatography make ideal DCS for binding drugs in the compositions of the present invention. Such resins are readily available, for example, from Rohm & Haas (Philadelphia, Pennsylvania) under the name Amberlite® and from Dow Chemical Co. (Midland, Michigan) under the name Dowex®. The average particle size of the commercially available forms of the resins is about 40 to 150 microns. As the particle size of the resin is critical, such commercially available particles are most conveniently reduced to a particle size range of about 1.0 to 25 microns by ball milling, according to known techniques. At least 95% of the resulting spheroidal particles must have a diameter less than 20 microns. The ion exchange resins will typically be present in an amount between about 0.05 and about 10.0

wt% and will have an average particle size diameter between about 1 and about 20 microns.

In addition to the above-described principal ingredients, the anti-glaucoma compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M® and other agents equally well-known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.001 and about 1.0 wt%. Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include: sodium chloride, potassium chloride, mannitol, dextrose, glycerin and propylene glycol. Such agents, if utilized, will typically be employed in an amount between about 0.1 and about 10.0 wt%.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The compositions are preferably aqueous, have a pH between 3.5 to 8.0 and an osmolality between 280 to 320 milliOsmoles per kilogram (mOsm/kg).

The compositions of the present invention may also comprise non-aqueous formulations such as: substantially non-aqueous liquids substantially non-aqueous semi-solid compositions and solid compositions or devices. The first class, substantially non-aqueous liquids, comprise a combination of calcium channel antagonist and IOP-lowering compound ("drug combination") dissolved or suspended in one or more of the following: vegetable and mineral oils, such as, liquid petrolatum, corn oil, castor oil, sesame oil and peanut oil; triglycerides, such as the capric/caprylic triglycerides commonly used in foods and cosmetics; liquid lanolin and lanolin derivatives; and perfluorohydrocarbons. The second class, semi-solid compositions, comprise a drug combination dissolved or suspended in

one or more of the following: various types of petrolatum, such as white, yellow, red and so on; lanolin and lanolin derivatives; gelled mineral oil having a hydrocarbon base, such as Plastibase®; petrolatum and ethylene carbonate mixtures; petrolatum in combination with surfactants and polyglycol, such as polyoxyl 40 stearate and polyethylene glycol.

The third class, solid compositions or devices, include non-erodible devices which are inserted into the conjunctival sac of the eye and later removed, such as the Alza-type diffusion or osmotic pressure controlled polymer membranes; and bioerodible polymers which do not have to be removed from the conjunctival sac, such as essentially anhydrous but water soluble polymers and resins (e.g., celluloses, polycarboxylic acids, and so on). Especially preferred are the bioerodible inserts described and detailed in US 4,540,408 (Lloyd) and US 4,730,013 (Bondi et al.), wherein drug combinations of the present invention would be entrained in a non-aqueous matrix consisting essentially of polyvinyl alcohol. The entire contents of these two patents are incorporated herein by reference.

The present invention is also directed to methods of treating glaucoma and other ophthalmic diseases and abnormalities. The methods comprise topically applying to the affected eye(s) of the patient a therapeutically effective amount of a composition according to the present invention. The frequency and amount of dosage will be determined by the clinician based on various clinical factors. The methods will typically comprise topical application of one or two drops (or an equivalent amount of a solid or semi-solid dosage form) to the affected eye one to two times per day.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. A topical ophthalmic composition for the treatment of glaucoma, comprising an ophthalmically effective combination of a compound which enhances vascular support of an ophthalmic organelle and a compound which lowers or controls intraocular pressure.

2. A topical ophthalmic composition for the treatment of glaucoma, comprising a combination of a calcium antagonist and a compound which lowers intraocular pressure, wherein the final composition concentration of the calcium antagonist is between about 0.0001 and about 10.0 wt% and the final composition concentration of the compound which lowers intraocular pressure is between about 0.00001 and about 10.0 wt%.

3. The composition of claim 1 or 2, further comprising an anionic, mucomimetic polymer, wherein the final composition concentration of the anionic, mucomimetic polymer is between about 0.05 and about 8.0 wt%.

4. The composition of claim 1 or 2, further comprising a gelling polysaccharide, wherein the final composition concentration of the gelling polysaccharide is between about 0.1 to about 3.0 wt%.

5. The composition of claim 1, 2, 3 or 4, further comprising a finely divided drug carrier substrate, wherein the final composition concentration of the finely divided drug carrier substrate is between about 0.05 and 10.0 wt%.

6. The composition of claim 2, 3, 4 or 5, wherein the final composition concentration of the calcium antagonist is between about 0.001 and about 5.0 wt%.

7. The composition of claim 6, wherein the final composition concentration of the calcium antagonist is between about 0.01 and about 2.5 wt%.

8. The composition of claim 2, 3, 4 or 5, wherein the final composition concentration of the compound which lowers intraocular pressure is between about 0.001 and about 5.0 wt%.

9. The composition of claim 8, wherein the final composition concentration of the compound which lowers intraocular pressure is between about 0.01 and about 2.5 wt%.

10. The composition of claim 2, 3, 4 or 5, wherein the calcium antagonist is selected from the group consisting of: AE 0047, AHR 5360C, AHR 12234C, AHR 16303B, AHR 16462B, AJ 2615, AJ 3941, AQ-AH-208-Cl, AR 12-456, alismol, amlodipine, anipamil, B 844-39, Bay-e-6927, Bay-k-9320, barnidipine, BBR 2160, belfosdil, benidipine, bepridil, bisaramil, BMY 20014, BMY 20064, BN 50149, BN 50175, BN 50394, BRL 3287A, buflomedil, butoprozine, caroverine, CD 349, CERM 11956, CGP 22442, CGP 26797, CGP 28392, CGP 28727, CGP 32413, CGS 19755, CI 951, cinnarizine, clentiazem, CNS 2103, COR 28-22, COR-2707C, COR 3752C, cronidipine, CRE 202, CRE 204, CRE 1005, CS 905, CV 159, D 2603, dagapamil, darodipine, desmethylverapamil, DHM9, DHP 218, diclofurime, diltiazem, diperdipine, diproteverine, dopropidil, dotarizine, EG 1088, elgodipine, emopamil, F-0401, fantofarone, FCE 24265, fedopamil, felodipine, feniline, flordipine, flunarizine, fostidil, FPL 62129, FR 46171, FRC 8411, FRG 8653, furaldipine, gallopamil, GOE 5057, GOE 5584-A, GOE 93007, GYKI 46544, HA 1004, HA 1077, HE-3-0346, HOE-166, Hoe 263, HP 406, israldipine, KB 2796, KP 873, KT 362, KW 3049, lacidipine, LAS 30356, LAS 30398, LAS 30538, LAS-Z077, LCB 2514, lidoflazine, LU 49938, manidipine, MCI 176, McN 5691, McN 6186, MCN 6497, MD 260792, MDL 143, MDL 12330A, MDL 16582A, MDL 72567, mepami, mepirodipine, mesudipine, minodipine, mioflazine, MJ 14712, MPC 1304, MPC 2101, N 20776, naltiazem, NB 818, NC 1100, NCO 700, NH 2250, NH 2716, NKY 722, NP 252, NZ 105, nicardipine, nictiazem, nifedipine,

nigludipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, OPC 13340, oxodipine, P 0285, palonidipine, P 1268, PD 122860, pelanserin, perhexiline, PF 244, pirprofurol, pimozide, PN 200-110, prenylamine, R 71811, Rec 15/2288, Rec-15/2375, RGH 2970, riodipine, Ro 18-3981, Ro 40-5967, ronipamil, RS 93007, RU 43945, RWJ 22726, RWJ 26899, RWJ 26902, ryanodine, S 312-d, S12968, S11568, S 830327, SA 2572, SA 2995, SA 3212, sagandipine, SC 30552, selodipine, semotiadil, SIM 6080, SKF 96365, SM 6586, sornidipine, SL 85.1016, SQ 31486, SQ 31765, SQ 31727, SQ 32321, SQ 32324, SQ 33351, SQ 33537, SR 33805, SUN 5647, SUN 6087, taludipine, tiapamil, TN 871, TR 2957, trapidil, UK 51656, UK 52831, UK 55444, verapamil, vinigrol, vintoperol, W 787, WAS 4206, WK 269, WY 27569, WY 44644, WY 44705, WY 46622, WY 47324, Y 19638, Y 208835, Y 22516, YC 114, YM 15430-1, YM 16151-4, YS 035, YS 161 and their pharmaceutically acceptable salts.

11. The composition of claim 10, wherein the calcium antagonist is selected from the group consisting of: bluflomedil, diltiazem, emopamil, felodipine, flunarizine, israldipine, lidoflazine, mioflazine, nimodipine, nifedipine, R-56865, R-58735 and their pharmaceutically acceptable salts.

12. The composition of claim 2, 3, 4 or 5, wherein the compound which lowers intraocular pressure is selected from the group consisting of: miotics, sympathomimetics, beta-blockers and carbonic anhydrase inhibitors.

13. The composition of claim 12, wherein the compound which lowers intraocular pressure is selected from the group consisting of: betaxolol, levobunolol, timolol, pilocarpine, carbachol, carteolol, acetylcholinesterase inhibitors, epinephrine, dipivalylepinephrine, α-methyl dipivalylepinephrine, clonidine, para-amino clonidine, acetazolamide, methazolamide, ethoxzolamide, MK 927, MK 507, AL04414, ALO4623 and ALO4862.

14. The composition of claim 13, wherein the compound which lowers intraocular pressure is selected from the group consisting of: timolol, betaxolol, levobunol, carteolol, pilocarpine, carbachol, MK 927, MK 507, AL04414, ALO4623, ALO4862, epinephrine, dipivalyl epinephrine, α-methyl dipivalylepinephrine, apraclonidine, clonidine.

15. Use of a pharmaceutical composition comprising a combination of a calcium antagonist and a compound which lowers intraocular pressure for the treatment of glaucoma, wherein the composition comprises between about 0.0001 and about 10.0 wt% of a calcium antagonist and between about 0.00001 and about 10.0 wt% of a compound which lowers intraocular pressure.

16. Use according to claim 15, wherein the composition further comprises between about 0.05 and about 8.0 wt% of an anionic, mucomimetic polymer.

17. Use according to claim 15, wherein the composition further comprises between about 0.1 to about 3.0 wt% of a gelling polysaccharide.

18. Use according to claim 15, 16 or 17, wherein the composition further comprises between about 0.05 and 10.0 wt% of a finely divided drug carrier substrate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04505

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K45/06; A61K9/06; A61K31/275; A61K47/32; A61K31/44; A61K47/36; A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X,Y	US,A,4 981 871 (M.B. ABELSON) 1 January 1991 see the whole document ---	1-18
X,Y	FR,A,2 585 574 (J. CORBIERE) 6 February 1987 see the whole document ---	1-18
X,Y	FR,A,2 593 395 (J. CORBIERE) 31 July 1987 see the whole document ---	1-18
X	EP,A,0 194 178 (SYNTHELABO) 10 September 1986 see page 2, line 7-11; claims ---	1,2,6-14

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04 AUGUST 1993	18. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ORVIZ DIAZ P.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 429 732 (ALCON LABORATORIES, INC.) 5 June 1991 cited in the application see claims ---	1-18
P,Y	EP,A,0 507 224 (ALCON LABORATORIES, INC.) 7 October 1992 cited in the application see claims ---	1-18
Y	BERKOW, R. (ED.), 'THE MERCK MANUAL OF DIAGNOSIS AND THERAPY'. 15TH EDITION, 1987, MERCK SHARP & DOHME RESEARCH LABORATORIES, RAHWAY, N.J., USA. see table 224-1 (pages 2236 and 2237) -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/ 04505

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-18 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compositions.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see following page ../..

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

2. Obscurities, inconsistencies,...

In absence of specific pharmacological examples and in view of the large number of compounds encompassed by the expressions in claims 1,2 and 12 and mentioned in claims 10, 11, 13 and 14, the search had to be limited, in principle, to the general concepts and to the compounds which, according to the general knowledge, are considered most representative (see PCT, ART. 6; Guidelines for Examination in the European Patent Office, Part B, Chapter II.7 last sentence and Chapter III.3.7).

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304505
SA 74135

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 04/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4981871	01-01-91	WO-A- 9207563	14-05-92
FR-A-2585574	06-02-87	None	
FR-A-2593395	31-07-87	None	
EP-A-0194178	10-09-86	FR-A- 2577802	29-08-86
		AU-A- 5402286	04-09-86
		JP-A- 61200917	05-09-86
EP-A-0429732	05-06-91	US-A- 4911920	27-03-90
		AU-B- 621692	19-03-92
		AU-A- 4575389	01-08-91
EP-A-0507224	07-10-92	AU-A- 1386392	01-10-92
		US-A- 5212162	18-05-93

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82